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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,495	02/28/2002	Chihiro Kusunoki	SHIMO13	2089

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EXAMINER	
LIETO, LOUIS D	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/937,495	**Applicant(s)** KUSUNOKI ET AL.	
	Examiner Louis D. Lieto	**Art Unit** 1632	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 31 May 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *None*.
   Claim(s) objected to: *None*.
   Claim(s) rejected: *15,16 and 18-23*.
   Claim(s) withdrawn from consideration: *None*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
12. ☒ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). 4/27/05
13. ☒ Other: See Continuation Sheet.

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Continuation of 13. Other:

The rejection of claims 15-17 and 18-23 under 35 USC § 112 is maintained. While applicants have amended the claims to read on only fusing a B cell from a transgenic mouse with a myeloma cell line they have not amended their claims to comply with the previous scope of enablement rejections set forth in the office actions of 8/30/204 and 3/31/205.

The rejection of claims 15-17 and 18-23 under 35 USC § 103 is maintained. Applicant's arguments have been fully considered but are not persuasive. Applicant argues that the rejection under 35 USC § 103 is inconsistent with the previous rejection under 35 USC § 112. Specifically that since it was argued that it was unpredictable for applicant to use any cell other than a myeloma cell to make hybridomas for the claimed invention it must also be unpredictable to introduce the exogenous sequences of Wood et al. to the transgenic hybridoma cell lines of Mendez et al. Applicant should note that the rejection under 35 USC § 112 was based on the failure of the specification to provide any guidance on how to produce hybridomas by fusing a B cell with any immortal cell line other than a myeloma cell line. Immortal cell lines include, fibroblasts, jurkat cells and antibody producing B cell lymphoma cell lines, amongst others. The only working example in the specification teaches fusing a B cell with a myeloma cell line (NSO-bs12) incapable of producing antibodies (Specification pg. 21).

The obviousness rejection under 35 USC § 103 is based on the teachings of Wood et al. of a method for producing a monoclonal antibody by introducing into a hybridoma containing an exogenous rearranged immunoglobulin heavy chain and an exogenous rearranged immunoglobulin light chain, a third exogenous DNA corresponding to the DNA encoding the immunoglobulin heavy chain, the culturing of said cell and the production of a functional monoclonal antibody. Wood et al. teaches that the object of the invention is to improve the levels of antibody expression (Wood1 et al., pgph 0006; Wood2 et al., col. 1, pgph 6), specifically through the optimization of heavy chain gene copy numbers (Wood1 et al., pgph 0008; Wood2 et al., col. 2, pgph 2). The technique of Wood et al. is a general technique that can be applied to any B-cell hybridoma, such as that taught by Mendez et al. (Mendez et al., pg. 151, col. 1 pgph 2). As previously stated in the office actions of 8/30/2004 and 3/31/2005 it would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to apply the teachings of Wood et al. to any b-cell hybridomas with endogenous rearranged heavy and light chains including the transgenic mouse B cell hybridoma taught by Mendez et al.

Next applicant argues that Wood et al. teaches the transfection of the hybridoma with multiple different sequences. It is noted that applicant's claimed invention is not limited to only nucleotide sequences that encode a heavy chain. Further, the relevant part of Wood et al. is to the transfection of a cell with "an exogenous nucleotide sequence which encodes a heavy chain polypeptide identical to the heavy chain polypeptide expressed by the endogenous immunoglobin heavy chain." Wood et al., teaches a mammalian B-cell hybridoma comprising DNA encoding an immunoglobulin heavy chain and an immunoglobulin light chain (Wood1 et al., pgph 0013; pgph 0021; Wood2 et al., col. 3, section II col. 4, pgph 3) and the introduction of a DNA encoding the identical immunoglobulin heavy chain (Wood1 et al, pgph 0024; Wood2 et al, col. 5, pgph 1). It would be obvious to the skilled practitioner that a DNA encoding an identical immunoglobulin heavy chain could be used to increase the antibody production of any hybridoma including the transgenic mouse B cell hybridoma taught by Mendez et al.

Finally, applicant argues that even if it were obvious to combine these references applicants have demonstrated improved unexpected results, specifically the increase in antibody production by about 2.6 times that of the untreated cells. However, the results of the claimed invention are not unexpected in view of the method taught by Wood et al., of increasing heavy chain gene copy number in hybridomas in order to increase monoclonal antibody production, an artisan would have expected to increase production of a monoclonal antibody by increasing heavy chain copy number. Specifically Wood et al. teaches that high expression levels of antibodies depends on optimizing the relative gene copy number of heavy and light chain DNAs and thus the relative expression levels (Wood1 et al., pgph 0008; Wood2 et al., col. 2, pgph 2). Applicant has the burden of establishing "that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance." See MPEP 716.02 b, c, d. This burden has not been met.

Applicant's arguments have been fully considered but are not found persuasive in overcoming the grounds of rejection as stated above and for reasons of record as set forth in the office actions of 8/30/2004 and 3/31/2005.

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